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TRANSLATION

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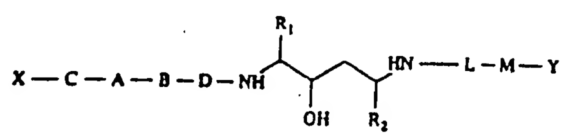
Title:

RETROISOSTERIC DIPEPTIDES, PROCESS FOR THEIR PRODUCTION AND THEIR USE AS RENIN INHIBITORS IN DRUGS

Summary

The invention concerns new retroisosteric dipeptides of the general formula I



in which X, A, B, D, L, M, Y, R_1 and R_2 have the meanings reported in the description, processes for their production and their use as renin inhibitors in drugs, especially in circulation-influencing drugs.

The invention concerns new retroisosteric dipeptides, processes for their production and their use as renin inhibitors in drugs, especially in circulation-influencing drugs.

Renin is a proteolytic enzyme produced predominantly in the kidneys and secreted into the plasma. It is known that renin splits off the decapeptide angiotensin I from angiotensinogen in vivo. Angiotensin I in turn is degraded in the lungs, kidneys or other tissues into the blood-pressure active octapeptide angiotensin II. The various effects of angiotensin II such as vasoconstriction, Na^+ retention in the kidneys, aldosterone liberation into the adrenals and tonus elevation of the sympathetic nervous system act synergistically in the sense of blood pressure elevation.

The activity of the renin-angiotensin system can be pharmacologically manipulated by inhibiting the activity of renin or the angiotensin conversion enzyme (ACE) and by blockade of angiotensin II receptors. The development of orally administered ACE inhibitors has thus led to new antihypertensives (cf. DOS 36 28 650, Am. J. Med. 77, 690, 1984). ACE, however, also acts on other substrates than angiotensin I, such as kinins. The latter may cause undesirable side-effects such as prostaglandin liberation and a series of behavioral and neurological effects. Besides this the ACE inhibitors cause accumulation of angiotensin I.

A specific approach is to intervene in the renin-angiotensin cascade at an early time, to wit, by inhibition of the acid aspartase renin which recognizes only angiotensinogen as a substrate.

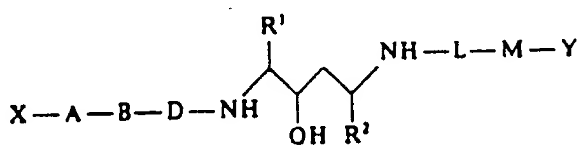
To date various types of renin inhibitors have been developed: renin-specific antibodies, phospholipids, peptides with the N terminal sequence of prorenin, synthetic peptides as substrate analogs and modified peptides. For

many renin inhibitors, in addition, the Lew-Val dipeptide is replaced by statin (EP 0 77 029) or by isosteric dipeptides (cf. US 44 24 207).

In addition, in PCT WO 88/02 374 renin inhibitors are included which contain retroisosteric dipeptide units as the protease-stable central core. Retroisosteric dipeptides have an amino group positioned at the head; the coupling to C-terminal amino acids leads to a reversal of the amide function (retroamide) which is characterized by a high metabolic stability with respect to enzymatic degradation.

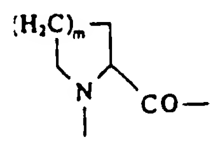
Through the process according to the invention new renin inhibitors have become available which surprisingly have a very high selectivity for human renin and good oral efficacy.

The invention concerns retroisosteric dipeptides of the general formula I

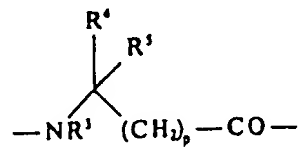


(I)

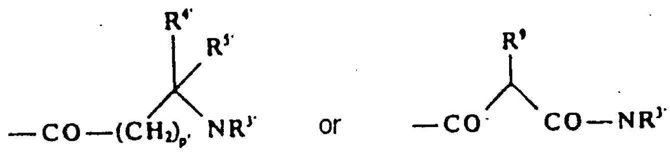
in which X stands for hydrogen or for alkoxy carbonyl or acyl in each case with up to 10 carbon atoms, A, B, and D are the same or different and in each case stand for a direct bond or for a radical of the formula



where m signifies the number 1 or 2 or stands for a group of the formula

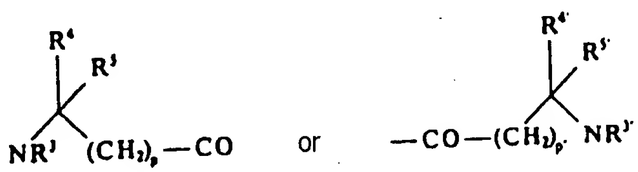


where p denotes the numbers 0, 1 or 2, R^3 stands for hydrogen, a straight chained or branched alkyl with up to 8 carbon atoms or phenyl, R^4 and R^5 are the same or different and signify a 3 to 8 membered heterocycle with up to 4 hetero-atoms from the series of nitrogen, oxygen or sulfur, cycloalkyl with 3 to 8 carbon atoms, or in each case stand for hydrogen or straight-chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by alkylthio with up to 6 carbon atoms, hydroxy, mercapto, guanidyl or by a group of the formula $-NR^6R^7$ or R^8-OC- where R^6 and R^7 are the same or different and denote hydrogen, straight chained or branched alkyl with up to 8 carbon atoms or phenyl, and R^8 denotes hydroxy, benzyloxy, alkoxy with up to 6 carbon atoms or the above-listed group $-NR^6R^7$, or alkyl which may possibly be substituted by aryl with 6 to 10 carbon atoms which in turn is substituted by hydroxy, halogen, nitro, alkoxy with up to 8 carbon atoms or by the group $-NR^6R^7$ in which R^6 and R^7 have the above-reported meaning or alkyl which is possibly substituted by a 5 or 6 membered nitrogen-containing heterocycle or indolyl where the corresponding -NH functions are possibly protected by alkyl with up to 6 carbon atoms or by an amino protective group, L and M are the same or different and stand for a direct bond or for a group of the formula



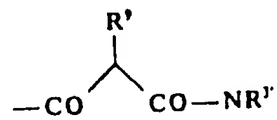
where p', $R^{3'}$, $R^{4'}$ and $R^{5'}$ have the above-reported meaning for p, R^3, R^4 and R^5 and may be the same as or different from them and R^9 is straight-chained or branched alkyl with up to 8 carbon atoms, in their D or L or as D,L isomer mixture, R^1 and R^2 are the same or different and stand for a straight chained or branched alkyl with up to 8 carbon atoms which is possibly substituted by cycloalkyl with 3 to 8 carbon atoms or aryl with 6 to 10 carbon atoms, Y stands for hydrogen or for a group of the formula -CO-R^{10} where R^{10} is a straight chained or branched alkyl with up 8 carbon atoms which is possibly substituted by pyridyl or phenyl, or a straight chained or branched alkoxy with up to 8 carbon atoms, or stands for the radical R^{10} where R^{10} has the above-reported meaning, with the qualification that either

a) at least one of the amino acid radicals A, B, D or L or M stands for a group of the formula



in which R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, p and p' have the above reported meaning and at least one of the substituents R^4, R^5, $R^{4'}$ or $R^{5'}$ stands for cyclopentyl or R^4 and R^5 or $R^{4'}$ and $R^{5'}$ in each case stand for methyl, or

b) L or M must stand for the group of the formula



in which R^9 and $R^{3'}$ have the above reported meaning, and their physiologically unobjectionable salts.

The term "amino protective group" within the context of the invention stands for the amino protective groups customarily used in peptide chemistry.

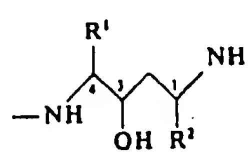
Here belong preferably: benzyloxycarbonyl, 4-bromobenzyl-oxycarbonyl, 2-chlorobenzyloxycarbonyl, 3-chlorobenzyloxy-carbonyl, 3,5-dimethoxybenzyloxycarbonyl, 4-methoxybenzyl-oxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrobenzylbenzyloxy-carbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-tri-methoxybenzyloxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, isopentoxycarbonyl, cyclohexoxycarbonyl, 2-chloroethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-trichloro-tert-butoxycarbonyl, benzohydryloxycarbonyl, bis-(4-methoxyphenyl) methoxycarbonyl, phenacyloxycarbonyl, 2-trimethylsilyl-ethoxycarbonyl, 2-triphenylsilylethoxycarbonyl, methyloxycarbonyl vinyloxycarbonyl, allyloxycarbonyl, fluorenyl-9-methoxycarbonyl, ethylthiocarbonyl, methylthiocarbonyl, butylthiocarbonyl, tert-butylthiocarbonyl, tert-butylthiocarbonyl, benzylthiocarbonyl, formyl, acetyl, propionyl, pivaloyl, 2-chloracetyl, 2-bromoacetyl, 2-idooacetyl, 2,2,2-trifluoroacetyl, 2,2,2-trichloroacetyl, benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl, 4-nitrobenzyl, 4-nitrobenzoyl, naphthylcarbonyl, phenoxyacetyl, adamantylcarbonyl, dicyclohexylphosphoryl, diphenylphosphoryl,

dibenzylphosphoryl, di-(4-nitrobenzyl)phosphoryl, phenoxyphenyl-phosphoryl, diethylphosphinyl, diphenylphosphinyl or phthaloyl.

Especially preferred amino protective groups are benzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 4-methoxy-benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrobenzyl-oxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, cyclohexaoxycarbonyl, 2-chloroetoxycarbonyl, phenoxyacetyl, naphthylcarbonyl, adamatylcarbonyl, phthaloyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-trichloro-tert-butoxycarbonyl, menthyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, fluororenyl-9-methoxycarbonyl, formyl, acetyl, propionyl, pivaloyl, 2-chloroacetyl, 2-bromoacetyl, 2,2,2-trifluoroacetyl, 2,2,2-trichloroacetyl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, isovaleroyl or benyloxymethylene.

The compounds according to the invention of general formula (I) have several asymmetrical carbon atoms. They may exist in the D or the L form independently of one another. The invention includes the optic antipodes as well as the isomer mixtures or racemates. Preferably the groups A, B, D, L and M independently of one another are present in the optically pure -- preferably in the L form.

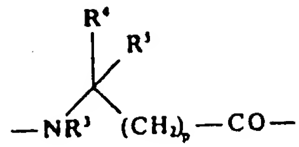
The group of the formula



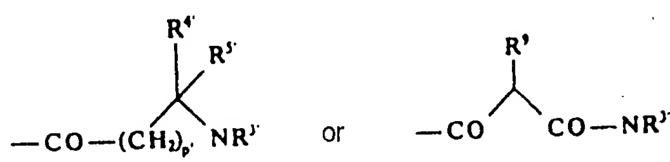
has 3 asymmetrical carbon atoms which, independently of one another, exist in the R or S configuration. This group is preferably in the 1R, 3S, 4S configuration, 1R, 3R, 4S configuration, 1S, 3R, 4S configuration or in the 1S, 3S, 4S configuration. Especially preferred 1S, 3S, 4S configuration and the 1R, 3S, 4S configuration which, depending on the nature of the substituent R^2, reflects the configuration of an L,L dipeptide.

The compounds of the general formula (I) according to the invention may exist in the form of their salts. These may be salts of the compounds according to the invention with inorganic or organic acids or bases. The acid addition products include preferably salt with hydrochloric acid, hydrobromic acid, hydroiodoic acid, sulfuric acid, phosphoric acid or with carboxylic acids such as acetic acid, propionic acid, oxalic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, adipic acid, malic acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, lactic acid, ascorbic acid, salicylic acid, 2-acetoxybenzoic acid, nicotinic acid, isonicotinic acid or sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, benzene sulfonic acid, toluenesulfonic acid, naphthalene-2-sulfonic acid or naphthalene disulfonic acid.

Preferred are compounds of general formula (I) in which
X stands for hydrogen or for alkoxycarbonyl or acyl in each case with up to 8 carbon atoms, A, B and D are the same or different and in each case stand for a direct bond or for proline or for a group of the formula



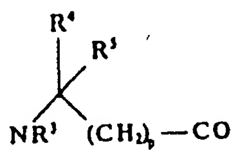
where p denotes the number 0 or 1, R^3 signifies hydrogen or a straight chained or branched alkyl with up to 6 carbon atoms or phenyl, R^4 and R^5 are the same or different and signify cyclopentyl or cyclohexyl, or hydrogen, phenyl or straight chained or branched alkyl with up to 6 carbon atoms which may possibly be substituted by naphthyl or phenyl which in turn may be substituted by fluoro, chloro, nitro or alkoxy with up to 6 carbon atoms, or signify alkyl (up to 6 C atoms) substituted by indolyl, imidazolyl, pyridyl, triazolyl or pyrazolyl, where the corresponding -NH functions are possibly protected by alkyl with up to 4 carbon atoms or by an amino protective group, L and M are the same different and stand for a direct bond or for a group of the formula



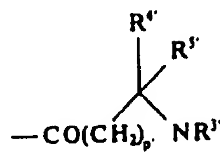
where p', $R^{3'}$, $R^{4'}$ and $R^{5'}$ have the above-reported meaning for p, R^3, R^4 and R^5 and are the same as or different from them and R^9 is a straight chained or branched alkyl with up to 6 carbon atoms, in their D or L form or as a D,L-isomer mixture, R^1 and R^2 are the same or different and stand for a straight chained or branched alkyl with up to 6 carbon atoms which is possibly substituted by cyclopropyl, cyclopentyl, cyclohexyl or phenyl, Y stands for hydrogen or for a group of the formula -CO-R^{10} where R^{10} is a straight chained or branched alkyl with up to 6 carbon atoms which is possibly substituted by

pyridyl or phenyl, or a straight chained or branched alkoxy with up to 6 carbon atoms, stands for the radical R^{10} where R^{10} has the above-reported meaning with the qualification that either

a) at least one of the amino acid radicals A, B, D or L or M stands for a group of the formula

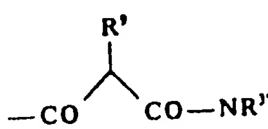


or



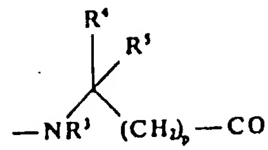
in which R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, p and p' have the above reported meaning and at least one of the substituents R^4, R^5, $R^{4'}$ or $R^{5'}$ stands for cyclopentyl or R^4 and R^5 or $R^{4'}$ and $R^{5'}$ in each case stand for methyl or

b) L or M must stand for the group of the formula

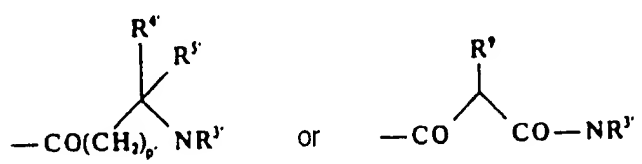


in which R^9 and $R^{3'}$ have the above reported meaning, and their physiologically unobjectionable salts.

Especially preferred are compounds of general formula (I) in which X stands for hydrogen or for alkoxycarbonyl or acyl in each case with up to 6 carbon atoms, A, B and D are the same or different and stand for a direct bond or for proline or for a group of the formula

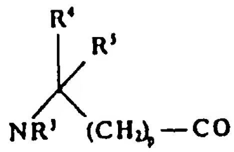


where p denotes the number 0 or 1, R^3 denotes hydrogen or methyl, R^4 and R^5 denotes cyclopentyl or straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by naphthyl or phenyl which in turn may be substituted by fluorine, chlorine or alkoxy with up to 4 carbon atoms, or substituted by imidazolyl, triazolyl, pyridyl or pyrazolyl, where the NH functions are possibly protected by methyl, benzyloxymethylene or t-butyloxycarbonyl (Boc), L and M are the same or different and stand for a direct bond or for a group of the formula

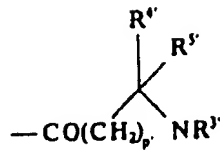


in which $R^{3'}$, $R^{4'}$ and $R^{5'}$ have the above reported meanings for R^3, R^4 and R^5 and are the same as or different from them, and R^9 is a straight-chained or branched alkyl with up to 4 carbon atoms, in there D or L form or as a D,L-isomer mixture, R^1 and R^2 are the same or different and stand for straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by cyclohexyl or phenyl, Y stands for hydrogen or for a group of the formula -CO-R^{10} where R^{10} is a straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by pyridyl or phenyl, or alkoxy with up to 4 carbon atoms, for the radical R^{10} where R^{10} has the above-reported meaning, with the qualification that either

a) at least one of the amino acid radicals A, B, D or L or M stands for a group of the formula

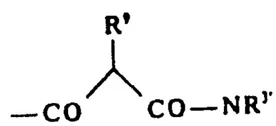


or



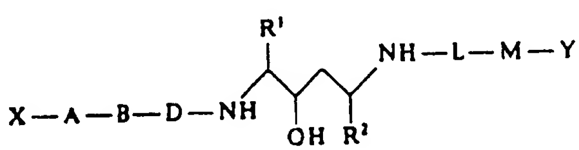
in which R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, p and p' have the above reported meaning and at least one of the substituents R^4, R^5, $R^{4'}$ or $R^{5'}$ stands for cyclopentyl or R^4 and R^5 or $R^{4'}$ and $R^{5'}$ in each case stand for methyl or

b) L or M must stand for the group of the formula



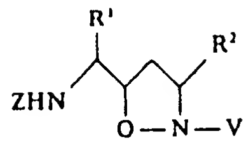
in which $R^{3'}$ and R^9 have the above reported meaning, and their physiologically unobjectionable salts.

The subject of the invention is also a process for the production of the compounds according to the invention of general formula (I)



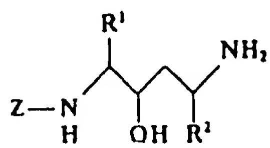
(I)

in which X, A, B, D, R^1, R^2, L, M and Y have the above-reported meaning characterized by the fact that compounds of general formula (II)



(II)

in which R^1 and R^2 have the above reported meaning, Z has the above-reported meaning of X but does not stand for hydrogen or stands for one of the above-listed amino protective groups, and V stands for a radical capable of being split off hydrogeno-lytically such as benzyl, are reduced initially by hydrogenolysis with opening of the isoxazolidine ring into the amino alcohols of general formula (III)



(III)

in which Z, R^1 and R^2 have the above-given meaning, if necessary subsequently condensed with compounds of general formula (IV) and (IVa)

HO-L'-M'-Y (IV)

HO-Y (IVa)

in which Y has the above-given meaning and the L' and M' have the above-reported meaning for L and M but do not stand simultaneously for a direct bond, if necessary in the presence of a water-removing accessory material and/or a base, and then, after the splitting off of the protective group Z, reacted by known methods with compounds of general formula (V)

Z'-B'-D'-OH (V)

in which B' and D' have the above-reported meaning of B and D but do not stand simultaneously for a direct bond, Z' has the above-reported meaning of Z and

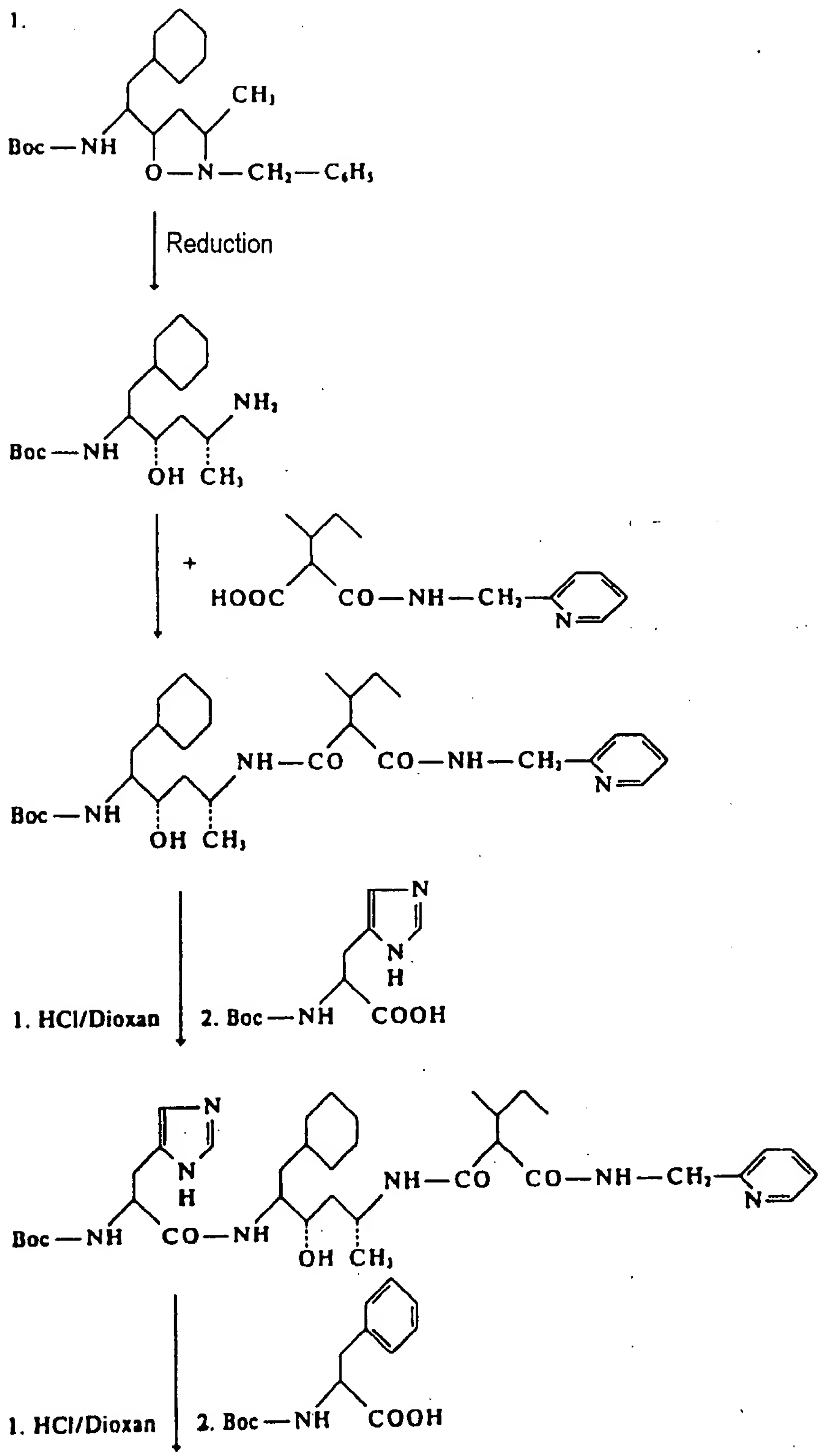
is the same as or different from it, and in a last step after the splitting off of the protective group Z' are reacted with compounds of formula (VI)

$$X\text{-}A'\text{-}OH \qquad (VI)$$

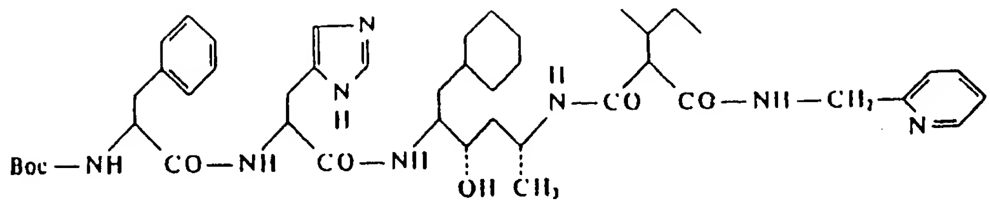
in which X has the above-reported meaning and A' the above-reported meaning of A but does not stand for a direct bond, if necessary in the presence of a base and inert organic solvents.

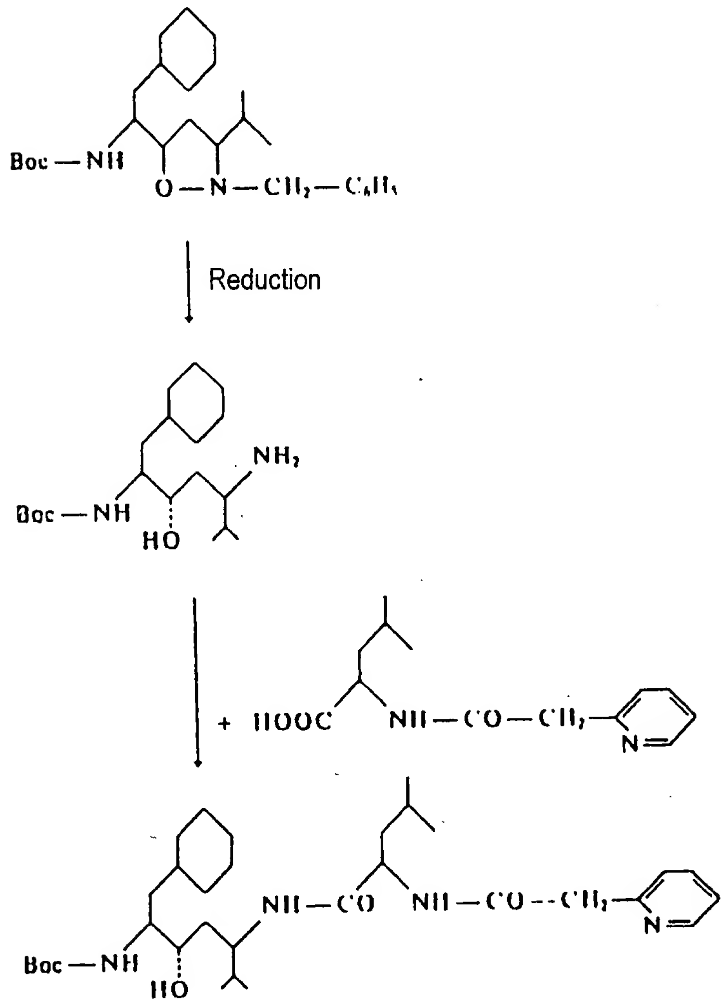
The process according to the invention may be explained by the following formulas as examples:

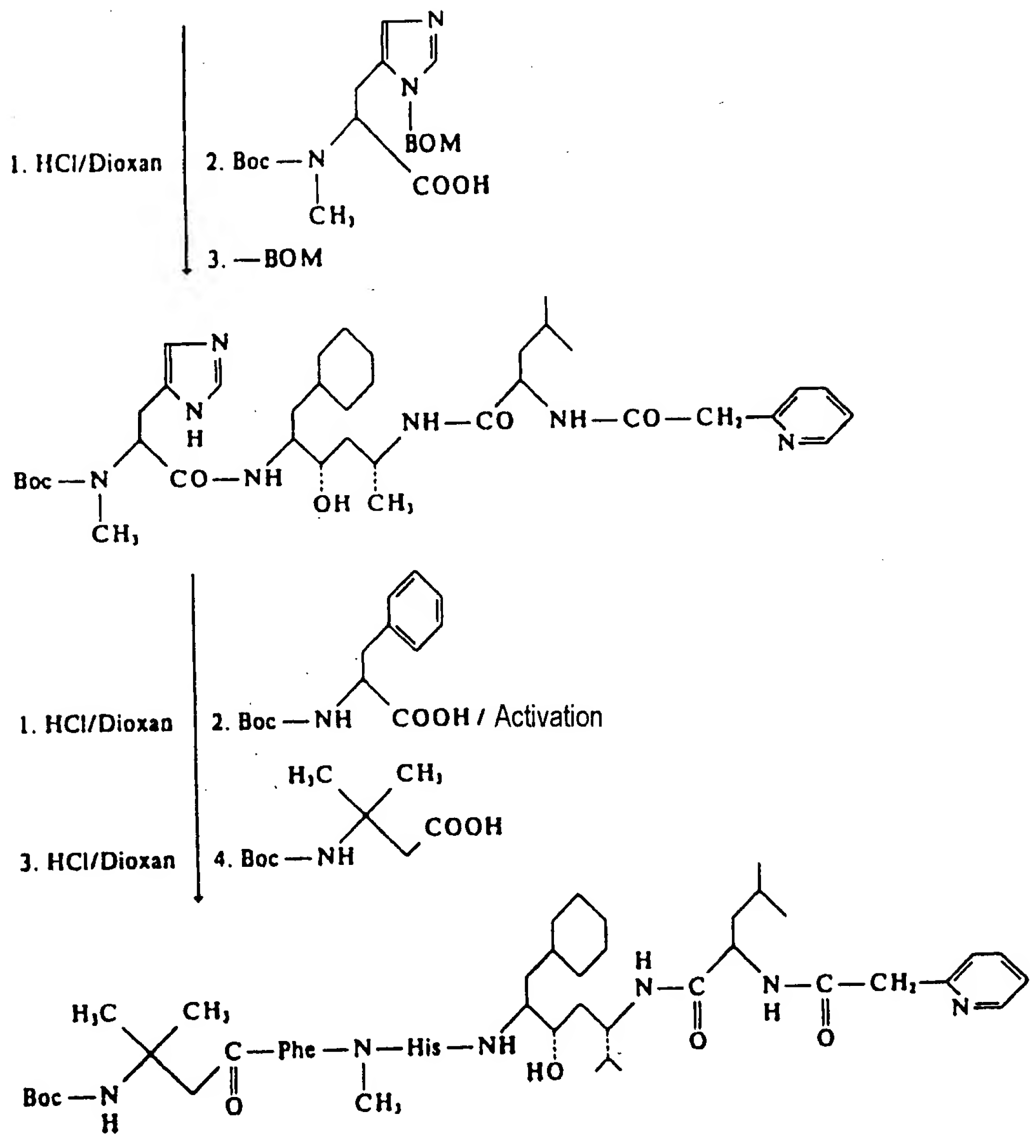
1.



CH3
Boc—NH
O—N—CH2—C6H5
Reduction
NH2
Boc—NH
OH CH3
+
HOOC
CO—NH—CH2—
N
NH—CO
CO—NH—CH2—
N
Boc—NH
OH CH3
N
N
H
1. HCl/Dioxan
2. Boc—NH
COOH
N
N
H
NH—CO
CO—NH—CH2—
N
Boc—NH
CO—NH
OH CH3
1. HCl/Dioxan
2. Boc—NH
COOH







Suitable solvents for all process steps are the conventional inert solvents which do not change under the conditions of the reaction. Here belong preferably organic solvents such as methanol, ethanol, propanol, isopropanol or ethers such as diethyl ether, glycol monomethyl or dimethyl ether, dioxane or tetrahydrofuran or hydrocarbons such as benzene, toluene, xylene, cyclohexane or petroleum fractions or halogenated hydrocarbons such as

methylene chloride, chloroform, carbon tetrachloride, or acetone, dimethylsulfoxide, dimethylformamide, hexamethyl-phosphoric acid triamide, acetic ester, pyridine, triethylamine or picoline. It is also possible to use mixtures of the above named solvents.

Especially preferred for the reduction are methanol and acetic acid ethyl ester, for the peptide couplings and the reaction with compounds of general formula (IV), (IVa), and (VI) -- methylene chloride.

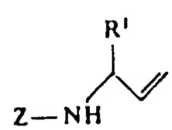
The reduction of the compounds of general formula (II) takes place either with the usual catalysts such as palladium hydroxide or palladium/carbon, preferably with palladium/carbon or via a catalytic transfer hydrogenation by the known method (cf. Tetrahedron 41, 3469 (1985), 3463 (1985), Synthesis 1987, 53).

The catalyst is used in a quantity of 0.05 to 1 mole, preferably from 0.1 to 0.5 mole relative to 1 mole of the compound of general formula (II).

The reduction is carried out in a temperature range from 40 to 160°C, preferably from 80 to 100°C.

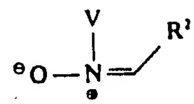
The reduction can be performed both at normal pressure and also at elevated or reduced pressure (e.g. 0.5 to 5 bar), preferably at normal pressure.

The compounds of general formula (II) are new and can be synthesized by reacting compounds of general formula (VII)



(VII)

in which Z has the above reported meaning, in a cycloaddition reaction with compounds of general formula (VIII)

 (VIII)

in which V and R^2 have the above-reported meaning.

Suitable solvents are the usual organic solvents which do not change under the reaction conditions. Here belong preferably alcohols such as methanol, ethanol, propanol, isopropanol, n-butanol or ethers such as diethyl ether, dioxane, tetra-hydrofuran, glycol, monoethyl or diethyl ether or hydrocarbons such as benzene, toluene, xylene or petroleum fractions or acetic acid n-butyl esters. n-Butyl, dioxane, acetic acid n-butyl ester, toluene, xylene or mesitylene are preferred.

The reaction can be conducted in a temperature range from 0 to 250°C, preferably at 100-170°C at normal or elevated pressure.

The compounds of general formula (VII) are well known or can be synthesized by ordinary methods [Chem. Pharm. Bull 30, 1921 (1982), Chem. Pharm. Bull 23, 3106 (1975), J. Org. Chem. 47, 3016 (1982)].

The compounds of general formula (VIII) are well known or can be synthesized by ordinary methods [J. J. Tufariello in 1,3-Dipolar Cycloaddition Chemistry, vol. 2, ed. A. Padwa, p. 83-168, John Wiley (1984), R. Huisgen, H. Seidel, J. Bruning, Chem. Ber. 102, 1102 (1969)].

The compounds of general formula (III) are well known [cf. PCT WO 88/02374] but can also be obtained by the above-reported new process via the

step of isoxazolidine (formula II) in the preferred stereochemistry and in better yields.

The compounds of general formulas (IV) and (V) are well known and can be produced by reacting a corresponding fragment consisting of one or more amino acid groupings with a free carboxyl group possibly existing in activated form, with a complementary fragment consisting of one or more amino acid groupings, with an amino group, if necessary in activated form, and are built up by repeating the process with the corresponding fragments until the desired peptides of the above-given general formulas are produced and subsequently splitting off protective groups if necessary or exchanging them for other protective groups (cf. Houben-Weyl, Methoden der organischen Chemie, Synthese von Peptiden II, 4 edition, vol. 15/1, 15/2, Georg Thieme Verlag, Stuttgart].

As accessory materials for the peptide coupling and introducing the radical Y (IV) and (IVa) one preferably uses condensation agents which may also be bases, especially if the carbonyl group is present in activated form as an anhydride. Preferably here the usual condensation agents such as carbodiimides, e.g. N,N-diethyl, N,N-dipropyl, N,N-diisopropyl, N,N-dicyclohexyl carbodiimides, N-(3-dimethylaminoisopropyl)-N-ethyl carbodiimide hydrochloride or carbonyl compounds such as carbonyl diimidazole or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium-3-sulfate or 2-tert-butyl-5-methylisoxazolium perchloride, or acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propane phosphonic acid anhydride, or isobutyl chloroformate or benzotriazolyloxy-tris(dimethylamino)phosphonium hexafluoro-phosphate.

As bases for the peptide coupling and in the reaction with compounds of general formula (VI) one may use alkali carbonates, e.g. sodium or potassium

carbonate or hydrogen carbonate, or organic bases such as trialkylamines, e.g. triethylamine, n-ethylmorpholine, N-methylpiperidine or N-methylmorpholine. Triethylamine is preferred.

The accessories and bases are used in a quantity of 0.5 moles to 4 moles, preferably 1 to 2 moles relative in each case to 1 mole of the compounds of general formula (VI).

The peptide coupling is performed in a temperature range from 0 to 100°C, preferably at 10 to 50°C and at normal pressure.

The reaction with compounds of general formula (IV), (IVa) and (VI) is conducted in a temperature range from -20 to +70°C, preferably at room temperature.

The reactions can be conducted both at normal pressure and also at elevated or reduced pressure (e.g. 0.5 to 5 bar), preferably at normal pressure.

The compounds of general formula (IVa) and (V) are well known.

The splitting off of the protective groups in each case before the individual peptide linkages is performed in the usual way under acid or basic conditions or reductively by catalytic hydrogenation, e.g. with Pd/C in organic solvents such as ethers, e.g. tetrahydrofuran or dioxane or alcohols such as methanol, ethanol or isopropanol [cf. Protective groups in organic synthesis, W. Greene, John Wiley & Sons New York, 1981; Chemistry and biochemistry of the amino acids, G. C. Barrett, Chapman and Hall, London, New York 1985].

In vitro test

The inhibitor strength of the peptides according to the invention against endogenous renin from human plasma is determined in vitro. Pooled human plasma is obtained with addition of ethylene diamine tetraacetic acid (EDTA) as the anticoagulant and stored at -20°C. The plasma renin activity (PRA) is determined as the rate of formation of angiotensin I from endogenous angiotensinogen and renin after incubation at 37°C. The reaction solution contains 150 µl plasma, 3 µl of 6.6% 8-hydroxyquinoline sulfate solution, 3 µl of 10% dimercaprol solution and 144 µl of sodium phosphate buffer (0.2 M, 0.1% EDTA, pH 5.6) with or without the materials according to the invention in various concentrations. The angiotensin I formed per unit time is determined with a radioimmunoassay (Sorin Biomedica, Italy). The percentage inhibition of the plasma renin activity is calculated by comparison of the substances claimed here. The concentration range in which the substances claimed here display a 50% inhibition of the plasma renin activity is between 10^{-4} and 10^{-9} M.

Examples of application

Example No.	% inhibition	IC_{50} (M)
2	100	1.3×10^{-6}
3	100	7.0×10^{-7}
7	100	2.7×10^{-7}
18	100	6.0×10^{-8}
21	100	1.5×10^{-8}

The new active principles can be transformed into the customary formulations in the usual way such as tablets, coated pills, pills, granulates, aerosols, syrups, emulsions, suspensions or solutions using inert nontoxic pharmaceutically suitable carriers or solvents. In this case the therapeutically active compound should always be present in a concentration of

about 0.5 to 90 wt. % of the total mixture, i.e. in quantities sufficient to achieve the reported dosage play.

The formulations are produced e.g. by adulterating the active principle with solvents and/or carriers, if necessary using emulsifiers and/or dispersing agents, where, e.g. in the case when water is used as the diluting agent, organic solvents may, if necessary, be used as accessory solvents.

Accessory materials include, for example:

Water, nontoxic organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. peanut oil/sesame seed oil), alcohols (e.g. ethyl alcohol, glycerine), carriers such as natural stone meal (e.g. kaolin, alumina, talcum, chalk), synthetic stone meal (e.g. highly dispersed silica, silicates), sugar (e.g. cane sugar, milk sugar and grape sugar), emulsifiers (e.g. polyoxyethylene fatty acid esters), polyoxyethylene fatty alcohol ethers (e.g. lignin, sulfite bleaches, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talcum, stearic acid and sodium sulfate).

They are administered by the usual route, preferably orally or parenterally, especially perlingually or intravenously. In the case of oral application the tablets, naturally, may contain besides the above-named carriers, also additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatins and the like. Furthermore, lubricants such as magnesium stearate, sodium lauryl sulfate and talcum may be used jointly for tabletting. In the case of aqueous suspensions the active principles may also be mixed with various taste enhancers or pigments besides the above-named accessories.

For the case of parenteral administration solutions of the active principle may be used employing suitable liquid carrier materials.

Generally it has been found to be advantageous in the case of intravenous administration to administer quantities from 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg of body weight in order to achieve effective results, and in the case of oral administration the dosage is about 0.01 to 20 mg/kg, preferably 0.1 to 10 mg/kg body weight.

Despite this it may occasionally be necessary to deviate from the above-stated quantities, depending on the body weight of the test animal or the form of application, but also on the basis of the animal species and its individual behavior relative to the drug or the nature of its formulation and the time or interval in which it is administered. Thus in some cases it may be sufficient to use less than the above-stated minimum quantity, while in other cases the upper limit mentioned will have to be exceeded. In the case of administration of large quantities it may be recommendable to distribute them over several single doses throughout the day. For administration in human medicine the same dosage variability is envisioned. Accordingly in such cases the above statements also apply here.

Appendix I

1. Amino acids

Generally the configuration is designated by placing an L or D in front of the amino acid abbreviation, in the case of the racemate by a D,L where for simplicity in the case of the L-amino acids the configuration designation can be omitted and then the explicit designation is given only in the case of the D form or the D,L mixture.

Ala	L-alanine
Arg	L-arginine
Cys	L-cysteine
Gln	L-gluthamine
Glu	L-glutamic acid
Gly	L-glycine
His	L-histidine
Ile	L-Isoleucine
Leu	L-leucine
Lys	L-lysine
Phe	Phenylalanine
Cpg	Cyclopentylglycine

2. Activation reagents and additives

HOBT	1-hydroxybenzotriazole
HOSU	N-hydroxysuccinimide
DCC	Dicyclohexylcarbodiimide
BOP	Benzotriqzolyloxy-tri-(dimethylamino)-phosphonium hexafluorophosphate
nPPA	n-propylphosphonic acid anhydride
NMM	N-methylmorpholine

3. Protective groups

Boc	tert. butoxycarbonyl
Z	Benzloxycarbonyl
AMP	2-aminomethylpyridine
BOM	Benzyloxymethylene
PAA	Pyridylacetic acid

Appendix II

The following eluent systems were used:

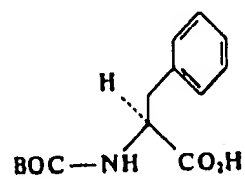
A - ether:hexane	2:8
B - ether:hexane	3:7
C - ether:hexane	4:6
D - ether:hexane	7:3
E - CH_2Cl_2:CH_3OH	95:5
F - CH_2Cl_2:CH_3OH	98:2
G - CH_2Cl_2:CH_3OH	90:10
H - CH_2Cl_2:CH_3OH:NH_3	95:5:0.1
I - CH_2Cl_2:CH_3OH:NH_3	90:90:0.1
J - Tol:Acetic acid ethyl ester:CH_3OH	25:75:1
K - nBuOH:HOAc:H_2O	8:2:2
L - Tol:Acetic acid ethyl ester	1:1
M - Tol:Acetic acid ethyl ester	1:3

For the compounds designated by x, ^{1}H-NMR data are available. The radical given in the examples of formula + stands for the tert.butyl group.

Initial compounds

Example I

BOC phenylalanine



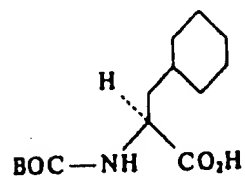
300 g (1.91 moles) of L-phenylalanine are suspended in 360 ml of dioxane and 360 ml of H_2O. 432.9 g (1.98 mole) of di-tert-butyl dicarbonate are added while stirring at Ph 9.8. The Ph is held constant with ca. 975 ml of 4 NaOH. After 16 h the reaction mixture is extracted with ether, the aqueous phase is adjusted to pH 3-4 with citric acid and subsequently extracted with 2 x ether, 2 x acetic ester. The organic phases are combined and washed 3 x with water. After centrifugation, crystallization from diethyl ether/hexane one obtains 291.6 g (60.7%).

m.p. 88-89°C

NMR (DMSO, 300 MHz), δ = 1.35 (s, 9H, $C(CH_3)_3$).

Example II

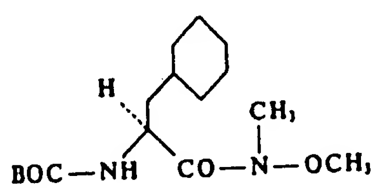
BOC-cyclohexylalanine



265 g (1.0 mole) of the compound from example I are dissolved in 2 l of methanol and hydrogenated over 20 g of 5% Rh/C for 5 h at 40 atm. The catalyst is pipetted off through celite, washed with methanol and the solution obtained concentrated. 271 g (100%) of example 6 are obtained.
NMR (DMSO, 300 Mhz), δ = 0.8-1.8 (m, 22H, cyclohexylmethylene, $C(CH_3)_3$.

Example III

BOC-cyclohexylalanine-N-methyl-O-methylhydroxamate



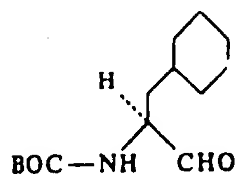
163.0 g (0.601 mole) of the compound of example II and 40.3 g (0.661 mole) of N,O-dimethylhydroxylamine are dissolved in 2 l of methylene chloride at room temperature. At 0°C, 303.5 g (3.005 moles) of triethylamine are added in drops (pH~8). At max. -10°C a 50% solution of 390.65 ml (0.601 mole) of n-PPa in methylene chloride are added in drops. It is warmed overnight to 25°C and stirred for 16 h. Then the reaction solution is concentrated, the residue mixed with 500 ml of saturated bicarbonate solution and stirred for 20 min. at 25°C. After extraction 3 times with acetic ester

the organic phase is dried over Na_2SO_4 and concentrated. Crude yield 178 g (94.6%). The raw material is chromatographed on silica gel (solvent F). Yield 136.6 g (72.3%).

NRM (DMSO, 300 MHz): δ = 1.37 (s, 9H, $C(CH_3)_3$), 3.08 (s, 3H, N-CH_3), 3.71 (s, 3H, O-CH_3).

Example IV

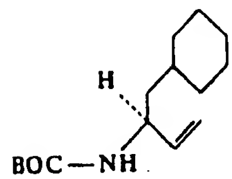
BOC-cyclohexylalaninal



Under nitrogen in a heated apparatus, 63.7 g (0.21 mole) of the compound of example III in 1.5 l of aloxated ether was dissolved, 10 g (0.263 mole) of $LiAlH_4$ added to it in portions at 0°C and then stirred for 20 min. at 0°C. Then a solution of 50 g (0.367 mole) of $KHSO_4$ in 1 l of H_2O was carefully added in drops at 0°C. The phases are separated, the aqueous phase extracted 3 times with diethyl ether 300 ml, the combined organic phases washed 3 times with 3 n HCl, 3 times with $NaHCO_3$ solution and twice with NaCl solution. The organic phase is dried over Na_2SO_4 and concentrated. Yield: 45 g (84.1%). The aldehyde is either further processed immediately or stored for 1 to 2 days at -24°C. NMR (DMSO, 300 MHz): δ = 9.4 (s, 1H, -CHO).

Example V

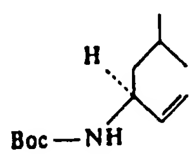
BOC-allylamine



14.6 g (35 mmole) of "instant ylide" (Fluka 69 500) are suspended in 90 ml of water-free tetrahydrofuran. With ice cooling at a reaction temperature between 20 and 25°C a solution of 9.0 g (35 mmole) of BOC cyclohexylalaninal in 45 ml of absolute tetrahydrofuran is added in drops. After 15 min. of stirring the reaction mixture is poured onto 250 ml of ice and extracted twice with 150 ml acetic ester/nhexane 3:1 each time. After drying over Na_2SO_4 and concentrating the residue is chromatographed on silica gel (solvent D). Yield: 3.2 g (40.0%).
EI-MS:m/z = 253 (0.1% M + H), 197 (9%).

Example VI

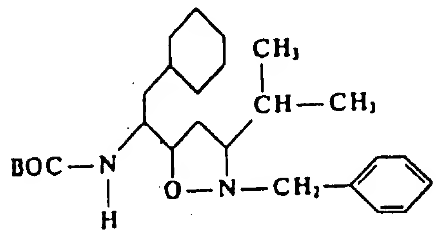
BOC-allylamine



Synthesized according to the instructions of example V with a 0.24 mole batch. Yield 25.92 g (50.6%).

Example VII

2-benzyl-3-(1-methyl)ethyl-5-(1-[Na-tert-butoxycarbonyl]amino-2-cyclohexyl)-ethylisoxazolidine



202.4 g (0.8 mole) of the compound of example V are dissolved in 1000 ml of mesitylene and warmed to 140°C on the water separator. At this temperature a mixture of 197 g (1.6 mole) of N-benzylhydroxylamine and 70.4 g (1.6 mole) of acetaldehyde in 800 ml of mesitylene are added in drops over 2 h. After 4 h and 8 h reaction time the same quantity of N-benzylhydroxylamine, acetaldehyde in mesitylene are added in drops. After a total of 16 h of reaction time the batch is concentrated, the residue mixed with diethyl ether and subsequently washed with 1 m $KHSO_4$ solution. After drying over Na_2SO_4 and concentrating it was chromatographed on silica gel (solvent B).

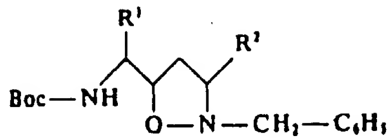
Yield: 168 g (52.2% of the theory).

Four diasteromers were obtained.

Diastereomer	Yield	DC,R_f(B)	^{1}H-NMR C-4-NH
a) 1S 3S 4S	11 g	0.42	6.37
b) 1R 3R 4S	10 g	0.29	6.57
c) 1R 3S 4S	69 g	0.25	6.41
d) 1S 3R 4S	34 g	0.18	6.63

The examples listed in Table I were prepared by analogy with the instructions of example VII.

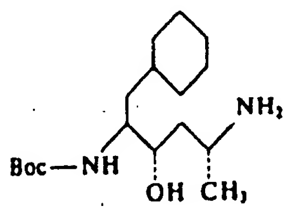
Table I



Example No.	R^1	R^2	FAB-MS M + H (%)
VIII IX	$-CH_2-CH(CH_3)_2$ $-CH_2-C_6H_{11}$	$-CH(CH_3)_2$ $-CH_3$	391 (55) isomer B 403 (51)

Example X

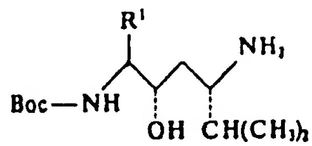
(2R, 4S, 5S)-2-amino-5-(tert-butoxycarbonylamino)-6-cyclohexyl-4-hydroxyhexane



18.1 g (45 mmole) of the compound of example IX (diastereomer C) are dissolved in 300 ml of methanol. After addition of 14.2 g (225 mmole) of ammonium formate it is rinsed intensively with N_2 and 3.6 g of palladium/carbon (10%) added. It is stirred for 3 h on reflux. After cooling the catalyst is filtered off, the solution concentrated, dissolved in acetic acid ethyl ester and washed twice with saturated bicarbonate solution. The organic phase is dried over sodium sulfate, filtered, concentrated and dried in the high vacuum. Yield: 11.36 g (80.3% of the theory). R_f = 0.27 (I).

The compounds listed in Table II were synthesized according to the instructions for example X.

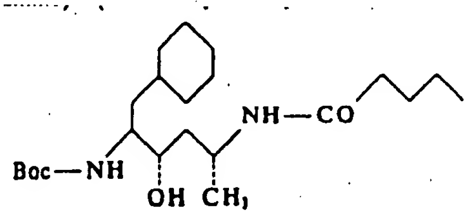
Table II



Example No.	R^1	FAB-MS M + H (%)
XI	$-CH_2-CH(CH_3)_2$	303 (95)
XII	$-CH_2-C_6H_{11}$	343 (100)

Example XIII

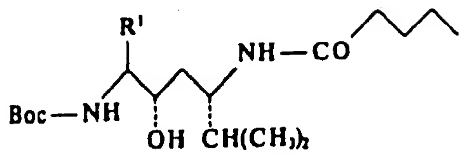
(2R, 4S, 5S)-2-(valerylamino)-5-(tert-butoxycarbonyl-amino)-6-cyclohexyl-4-hydroxyhexane.



6.6 g (21 mmole) of the compound of example X are dissolved in 500 ml of methylene chloride. With exclusion of moisture ($CaCl_2$ pipe) a solution of pentanic acid anhydride [prepared from 2.16 g (21 mmole) of pentanic acid and 2.16 g (10.5 mmole) of dicylcohexylcarbodiimide in 50 ml of methylene chloride, filtration] in methylene chloride are added at room temperature. After 3 h it is concentrated, absorbed in acetic acid ethyl ester, washed with saturated bicarbonate solution and dried over sodium sulfate. After filtration and concentration it is dried in the high vacuum. Yield: 8.0 g (95.2%) of the theory). R_f = 0.74 (G). FAB-MS:m/z = 421 (12%, N + Na).

The compounds listed in Table III were synthesized according to the instruction for example XIII.

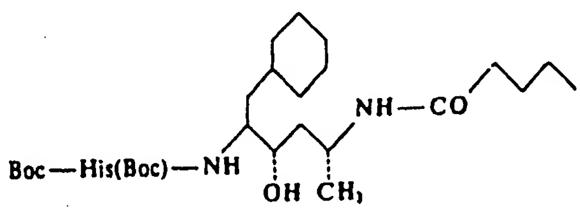
Table III



Example No.	R^1	FAB-MS M + H (%)	DC
XIV XV	$-CH_2-CH(CH_3)_2$ $-CH_2-C_6H_{11}$	387 (100) 327 (3% M + H-Boc)	

Example XVI

(2R, 4S, 5S)-5-(valerylamino)-5-[Nα-(tert-butoxycarbonyl)-Nπ-(tert-butoxycarbonyl)-L-histidyl]amino-6-cyclohexyl-4-hydroxyhexane



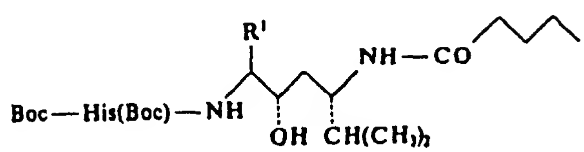
7.57 g (19 mmole) of the compound of example XIII are stirred in 70 ml of 4n hydrochloric acid/dioxane for 30 min. with exclusion of moisture. The solution is concentrated, mixed with diethyl ether and concentrated until dry. After drying in the high vacuum, 5.54 g (16.5 mmole) of the corresponding hydrochloride 1.46 g (33 mmole) of HOBT and 5.86 g (16.5 mmole) of Boc-His(Boc)OH in 500 ml of methylene chloride are dissolved. After cooling to 0°C, it is adjusted to pH 8.5 with N-methylmorpholine, and 3.57 g (17.3 mmole) of dicyclohexyl-carbodiimide are added. After 16 h at 20°C the urea is filtered off, the solution concentrated, absorbed in acetic acid ethyl ester

and washed with saturated bicarbonate solution. After drying over sodium sulfate it is concentrated and dried in the high vacuum. Yield: 8.33 g (79.5% of the theory). R_f = 0.61 (G).

FAB-MS:m/z = 636 (79%, M + H).

The examples listed in Table IV were synthesized according to the instructions for example XVI.

Table IV

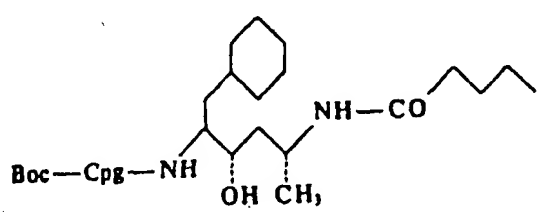


Example No.	R^1	FAB-MS M + H (%)
XVII	$-CH_2-CH(CH_3)_2$	624 (16)
XVIII	$-CH_2-C_6H_{11}$	670 (44, M + Li)

Examples of synthesis

Example 1

(2R, 4S, 5S)-2-(valerylamino)-5-[Nα-(tert-butoxycarbonyl)-L-cyclopropylglycyl]amino-6-cyclohexyl-4-hydroxyhexane



5.6 g (24.4 mmole) of BocCpgOH are dissolved in 50 ml of absolute tetrahydrofuran. After addition of 2.7 ml (24.4 mmole) of N-methylmorpholine, at -20°C, 3.2 ml (24.4 mmole) of chloroformic acid isobutyl ester are added in

drops and stirred for 15 min. at -20°C. To this solution 5.45 g (16.3 mmole) of the compound of example XIII and 1.8 ml (16.3 mmole) of N-methylmorpholine in 50 ml of tetrahydrofuran-water 1:1 are added in drops and warmed within 30 min. to 20°C. After another 30 min. the reaction solution is concentrated, added to 1 liter of diethyl ether and cooled to 0°C. After 16 h 4.6 g (54.0%) of crystals are pipetted off. The mother liquor is extracted with diethyl ether, then washed with saturated bicarbonate solution, dried over sodium sulfate, concentrated and dried in the high vacuum. 6 g of a yellow oil are obtained which is chromatographed on silica gel (E).

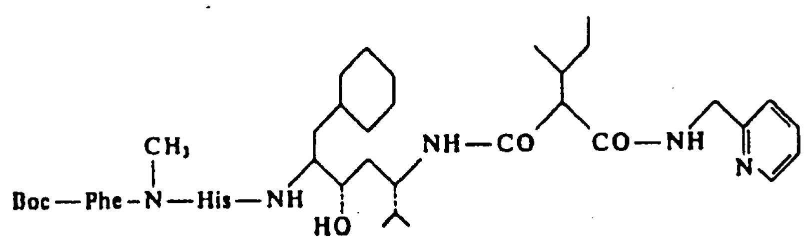
Yield: 3.31 g (38.8% of the theory).

R_f = 0.79 (G).

FAB-MS:m/z = 524 (38%, M + H).

Example 2

(3S, 5S, 6S)-3-[Nα-[Na-(2-pyridylacetyl)-D-isoleucyl-amino]-6-[Nα-[Nα-(tert-butoxycarbonyl)-L-phenylalanyl]-methyl-L-histidyl]-amino-7-cyclohexyl-5-hydroxy-2-methylheptane



351.5 mg (0.25 mmole) of N-methyl-His-BOM protected inhibitor are dissolved in 5 ml of methanol. After addition of 319 mg (5 mmole) of ammonium formate and 50 mg of 10% Pd/C it is stirred for 4 h at 60°C. Then the catalyst is filtered off through kieselguhr and the filtrate concentrated. The residue is absorbed in acetic ester, washed twice with saturated sodium

hydrogen carbonate solution and dried over sodium sulfate. 209.6 mg (96%) of crude material are obtained which is separated by HPLC (Vydac 218 TP, gradient 25-35% CH_3CN 0.05% TFE in 40 min: flow 10 ml/min).

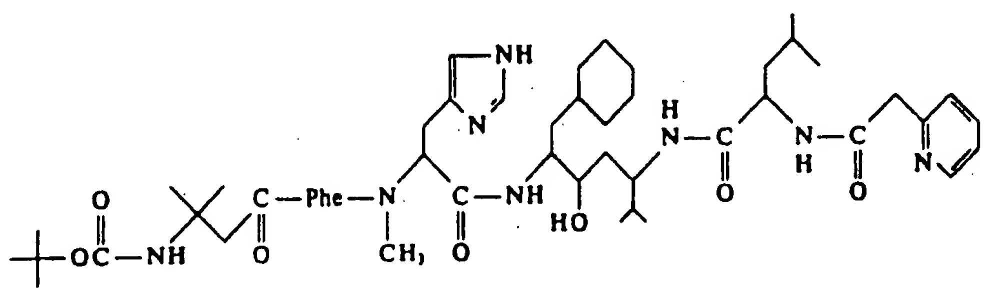
FAB-MS: m/z=895 (18%, M+Na),

873 (16%, M+N),

EF (MW): $C_{48}H_{72}N_8O_7$ (873.16)

Example 3

(3S, 5S, 6S)-3-[Nα-[Nα-(2-pyridylacetyl)-D-isoleucylamino]-6-[Nα-[Nα-[Nβ-(tert-butoxycarbonylamino)-3-methylpropanoyl]-L-phenylalanyl]-L-histidyl-amino-7-cyclohexyl-5-hydroxy-2-methylheptane



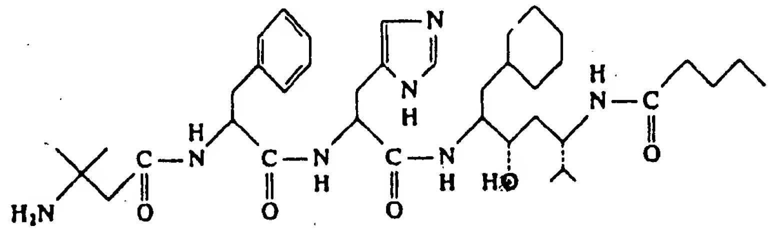
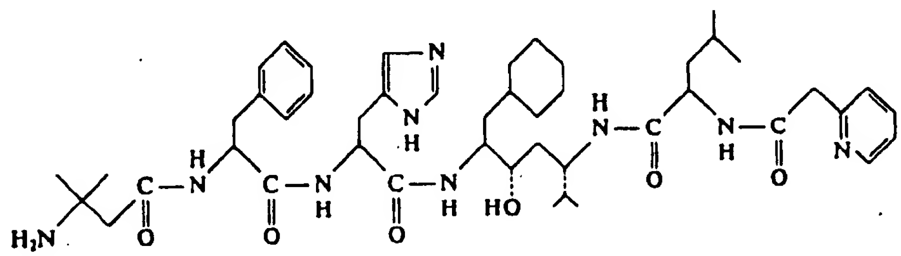
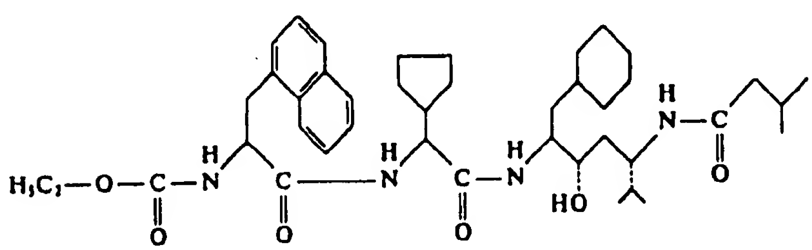
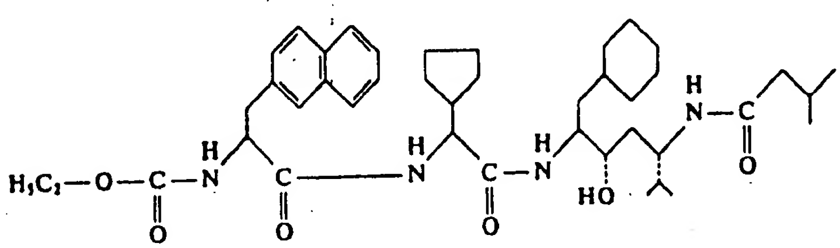
240 mg (0.03 mmole) of the deblocked inhibitor and 71.6 mg (0.33 mmole) of tert.butyloxycarbonyl-β-valine are suspended in 10 ml of absolute tetrahydrofuran. After addition of 91.8 mg (0.6 mmole) of HOBT the pH is adjusted to 8 with N-methylmorpholine and 68 mg (0.33 mmole) of DCC added at 0°C. After 16 h of reaction the urea is filtered off and the filtrate concentrated. The residue is absorbed in acetic ester and washed with saturated bicarbonate solution. The organic phase is dried over sodium sulfate. 227.3 mg (80%) of crude material are obtained, of which 80 mg are separated by preparative HPLC (Vydac 218 TP, gradient 35-70% CH_3CN 0.05% TFE in 40 min: flow 10 ml/min).

FAB-MS: m/z=972 (25%, M+H),

EF (MW): $C_{53}H_{81}N_9O_8$ (972.29)

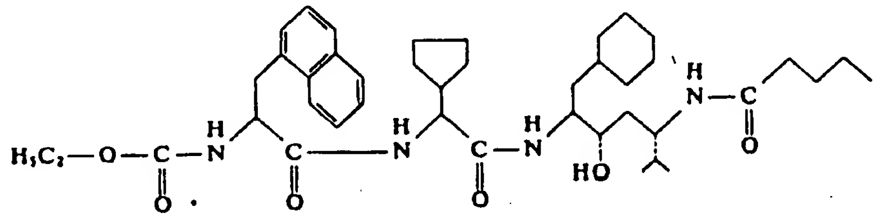
The examples listed in Table 1 were prepared according to the instructions of examples 1, 2, and 3:

Table I

Ex. No.	Formula
4	 NMR: x FAB-MS: 682 (5%, M + H) Empirical formula: $C_{37}H_{59}N_7O_5$ DC: HPLC
5	 NMR: x FAB-MS: 830 (38%, M + H) Empirical formula: $C_{45}H_{67}N_9O_6$ R_f = 0,46 (I)
6	 NMR: x FAB-MS: 721 (55%, M + H) Empirical formula : $C_{42}H_{64}N_4O_6$ R_f = 0,17 (E)
7	 NMR: x FAB-MS: 721 (100%, M + H) Empirical formula: $C_{42}H_{64}N_4O_6$ R_f = 0,26 (G)

Ex. No.	Formula

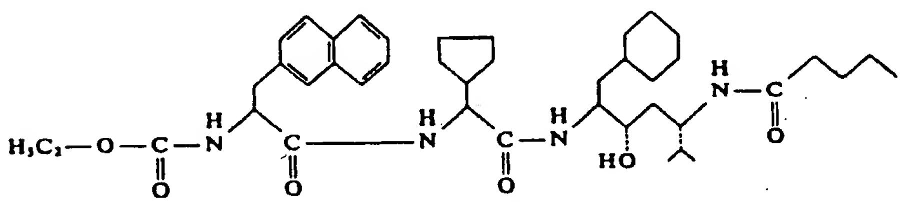
8



NMR: x
FAB-MS: 721 (60%, M+H)

Empirical formula: $C_{42}H_{64}N_4O_6$
R_f = 0,58 (G)

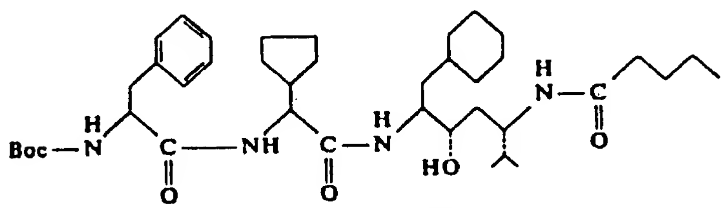
9



NMR: x
FAB-MS: 721 (100%, M+H)

Empirical formula: $C_{42}H_{64}N_4O_6$
R_f = 0,52 (G)

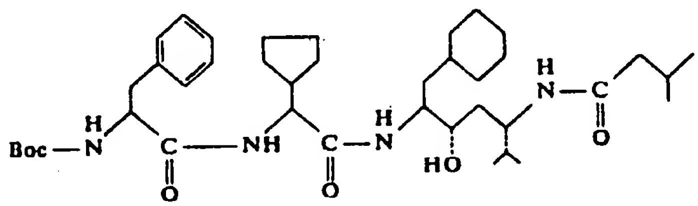
10



NMR: x
FAB-MS: 699 (100%, M+H)

Empirical formula: $C_{40}H_{66}N_4O_6$

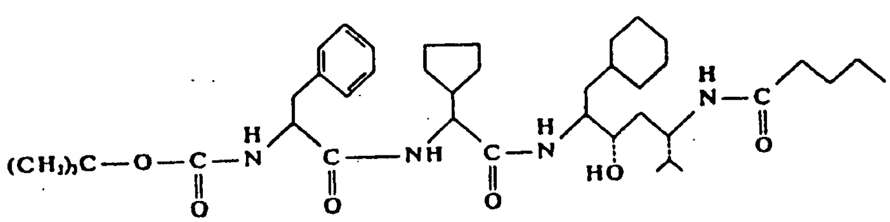
11



NMR: x
FAB-MS: 699 (73%, M+H)

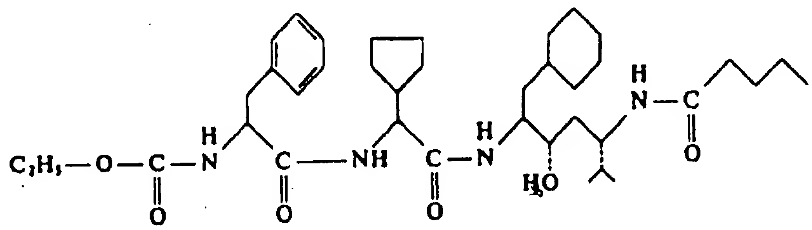
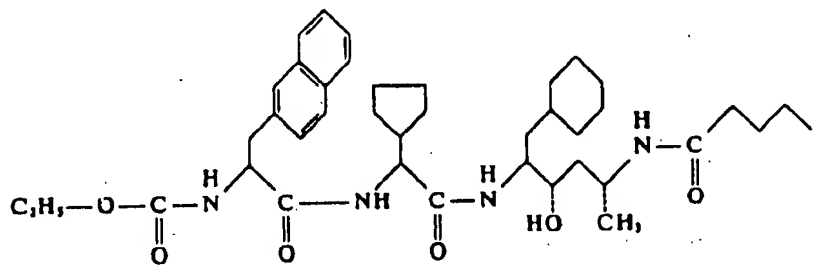
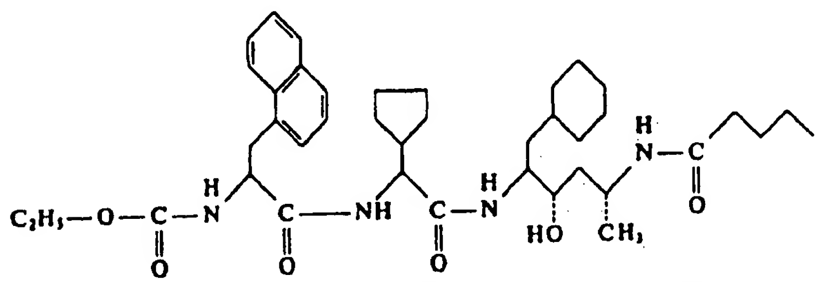
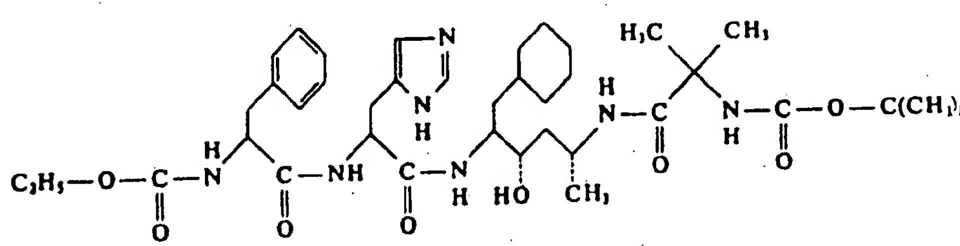
Empirical formula: $C_{40}H_{66}N_4O_6$

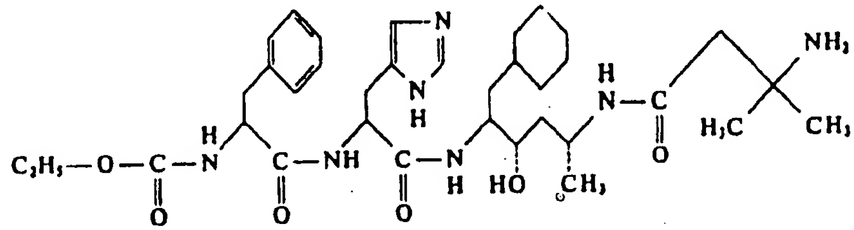
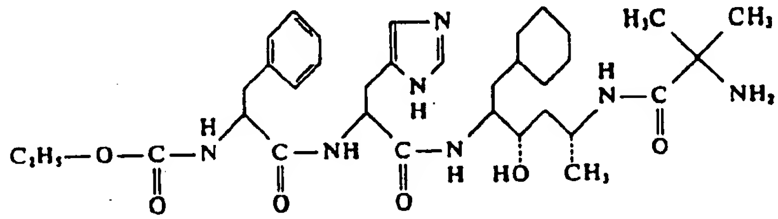
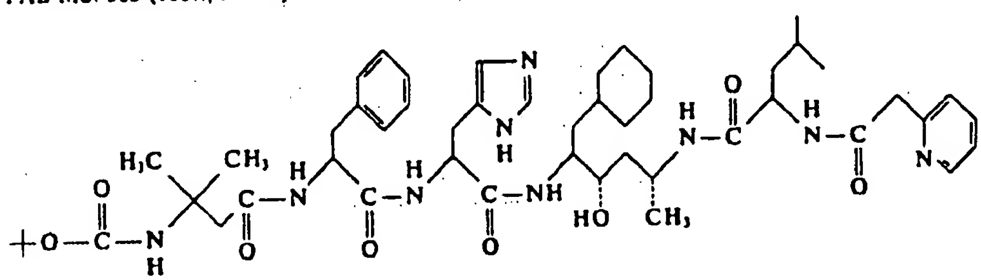
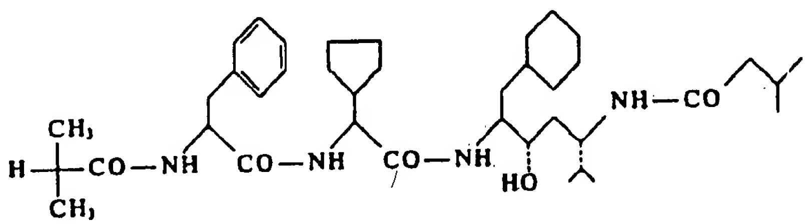
12

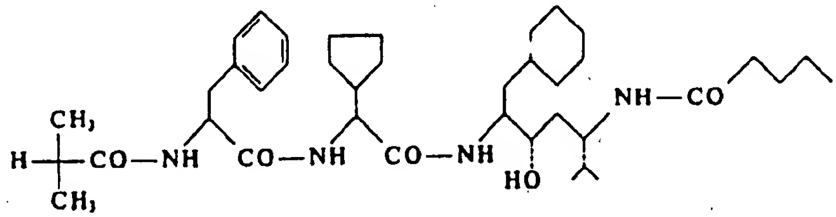
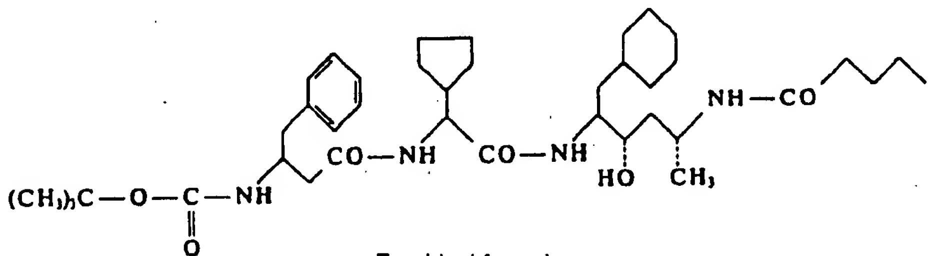


NMR: x
FAB-MS: 671 (38%, M+H)

Empirical formula: $C_{38}H_{62}N_4O_6$
R_f = 0,48 (I)

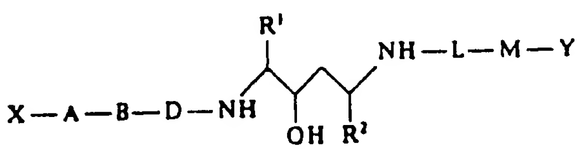
Ex. No.	Formula
13	 NMR: x FAB-MS: 643 (40%, M + H) Empirical formula : $C_{36}H_{58}N_4O_6$ R_f = 0,49 (I)
14	 NMR: x FAB-MS: 693 (87%, M + H) Empirical formula : $C_{40}H_{60}N_4O_6$ R_f = 0,55 (I)
15	 NMR: x FAB-MS: 693 (100%, M + H) Empirical formula : $C_{40}H_{60}N_4O_6$ R_f = 0,52 (I)
16	 NMR: x FAB-MS: 762 (100%, M + H) Empirical formula : $C_{39}H_{63}N_7O_8$ R_f = 0,52 (E)

Ex. No.	Formula
17	
	NMR: x FAB-MS: 676 (100%, M + Li) Empirical formula: $C_{35}H_{55}N_7O_6$ R_f = 0,06 (I)
18	
	NMR: x FAB-MS: 565 (100%, M + H) Empirical formula: $C_{34}H_{53}N_7O_6$ R_f = 0,05 (I)
19	
	NMR: x FAB-MS: 930 (85%, M + H) Empirical formula: $C_{50}H_{75}N_9O_8$ R_f = 0,48 (I)
20	
	NMR: x FAB-MS: 669 (60%, M + H) Empirical formula: $C_{39}H_{64}N_4O_5$ R_f = 0,40 (G)

Ex. No.	Formula
21	
	NMR: x FAB-MS: 669 (100%, M+H) Empirical formula : $C_{39}H_{64}N_4O_5$ R_f = 0,59 (G)
22	
	NMR: x FAB-MS: 691 (100%, M+Li) Empirical formula : $C_{39}H_{64}N_4O_6$ R_f = 0,46 (G)

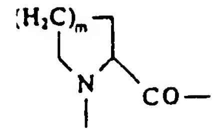
Claims

1. Retroisosteric dipeptides of the general formula I

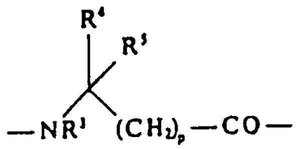


(I)

in which X stands for hydrogen or for alkoxy carbonyl or acyl in each case with up to 10 carbon atoms, A, B, and D are the same or different and in each case stand for a direct bond or for a radical of the formula

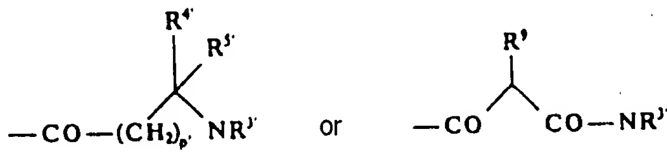


where m signifies the number 1 or 2 or stands for a group of the formula



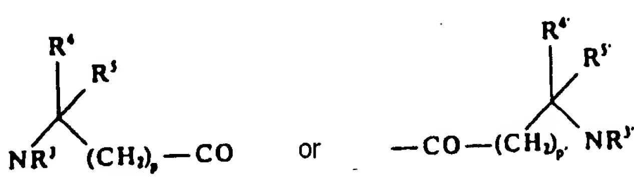
where p denotes the numbers 0, 1 or 2, R^3 stands for hydrogen, a straight chained or branched alkyl with up to 8 carbon atoms or phenyl, R^4 and R^5 are the same or different and signify a 3 to 8 membered heterocycle with up to 4 hetero-atoms from the series of nitrogen, oxygen or sulfur, cycloalkyl with 3 to 8 carbon atoms, or in each case stand for hydrogen or straight-chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by alkylthio with up to 6 carbon atoms, hydroxy, mercapto, guanidyl or by a group of the formula $-NR^6R^7$ or R^8-OC- where R^6 and R^7 are the same or different and denote hydrogen, straight chained or branched alkyl with up to 8 carbon atoms or phenyl, and R^8 denotes hydroxy, benzyloxy, alkoxy with up to 6 carbon atoms or the above-listed group $-NR^6R^7$, or alkyl which may possibly be substituted by aryl with 6 to 10 carbon atoms which in turn is substituted by hydroxy, halogen, nitro, alkoxy with up to 8 carbon atoms or by the group $-NR^6R^7$ in which R^6 and R^7 have the above-reported meaning or alkyl which is possibly substituted by a 5 or 6 membered nitrogen-containing heterocycle or indolyl where the corresponding -NH functions are possibly protected by alkyl with up

to 6 carbon atoms or by an amino protective group, L and M are the same or different and stand for a direct bond or for a group of the formula



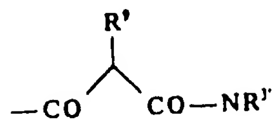
where p', $R^{3'}$, $R^{4'}$ and $R^{5'}$ have the above-reported meaning for p, R^3, R^4 and R^5 and may be the same as or different from them and R^9 is straight-chained or branched alkyl with up to 8 carbon atoms, in their D or L or as D,L isomer mixture, R^1 and R^2 are the same or different and stand for a straight chained or branched alkyl with up to 8 carbon atoms which is possibly substituted by cycloalkyl with 3 to 8 carbon atoms or aryl with 6 to 10 carbon atoms, Y stands for hydrogen or for a group of the formula -CO-R^{10} where R^{10} is a straight chained or branched alkyl with up 8 carbon atoms which is possibly substituted by pyridyl or phenyl, or a straight chained or branched alkoxy with up to 8 carbon atoms, or stands for the radical R^{10} where R^{10} has the above-reported meaning, with the qualification that either

a) at least one of the amino acid radicals A, B, D or L or M stands for a group of the formula



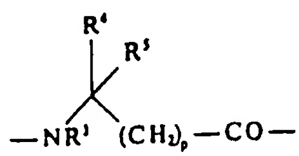
in which R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, p and p' have the above reported meaning and at least one of the substituents R^4, R^5, $R^{4'}$ or $R^{5'}$ stands for cyclopentyl or R^4 and R^5 or $R^{4'}$ and $R^{5'}$ in each case stand for methyl, or

b) L or M must stand for the group of the formula

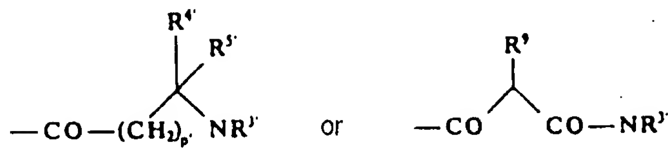


in which R^9 and $R^{3'}$ have the above reported meaning, and their physiologically unobjectionable salts.

2. Compounds of general formula (I) as in claim 1 in which X stands for hydrogen or for alkoxycarbonyl or acyl in each case with up to 8 carbon atoms, A, B and D are the same or different and in each case stand for a direct bond or for proline or for a group of the formula

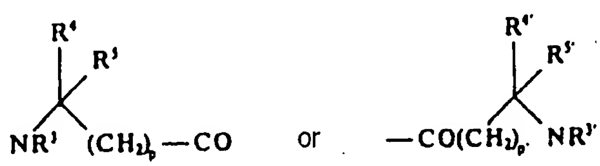


where p denotes the number 0 or 1, R^3 signifies hydrogen or a straight chained or branched alkyl with up to 6 carbon atoms or phenyl, R^4 and R^5 are the same or different and signify cyclopentyl or cyclohexyl, or hydrogen, phenyl or straight chained or branched alkyl with up to 6 carbon atoms which may possibly be substituted by naphthyl or phenyl which in turn may be substituted by fluoro, chloro, nitro or alkoxy with up to 6 carbon atoms, or signify alkyl (up to 6 C atoms) substituted by indolyl, imidazolyl, pyridyl, triazolyl or pyrazolyl, where the corresponding -NH functions are possibly protected by alkyl with up to 4 carbon atoms or by an amino protective group, L and M are the same different and stand for a direct bond or for a group of the formula



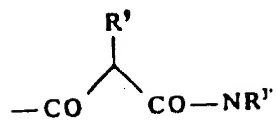
where p', $R^{3'}$, $R^{4'}$ and $R^{5'}$ have the above-reported meaning for p, R^3, R^4 and R^5 and are the same as or different from them and R^9 is a straight chained or branched alkyl with up to 6 carbon atoms, in their D or L form or as a D,L-isomer mixture, R^1 and R^2 are the same or different and stand for a straight chained or branched alkyl with up to 6 carbon atoms which is possibly substituted by cyclopropyl, cyclopentyl, cyclohexyl or phenyl, Y stands for hydrogen or for a group of the formula -CO-R^{10} where R^{10} is a straight chained or branched alkyl with up to 6 carbon atoms which is possibly substituted by pyridyl or phenyl, or a straight chained or branched alkoxy with up to 6 carbon atoms, stands for the radical R^{10} where R^{10} has the above-reported meaning with the qualification that either

a) at least one of the amino acid radicals A, B, D or L or M stands for a group of the formula



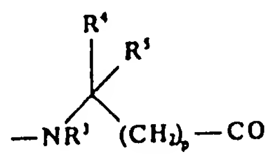
in which R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, p and p' have the above reported meaning and at least one of the substituents R^4, R^5, $R^{4'}$ or $R^{5'}$ stands for cyclopentyl or R^4 and R^5 or $R^{4'}$ and $R^{5'}$ in each case stand for methyl or

b) L or M must stand for the group of the formula

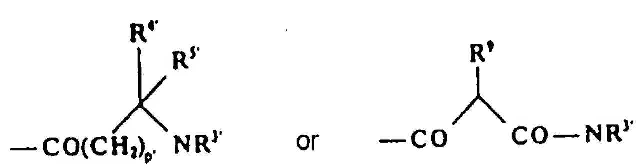


in which R^9 and $R^{3'}$ have the above reported meaning, and their physiologically unobjectionable salts.

3. Compounds of general formula 1 according to claim 1 in which X stands for hydrogen or for alkoxycarbonyl or acyl in each case with up to 6 carbon atoms, A, B and D are the same or different and stand for a direct bond or for proline or for a group of the formula

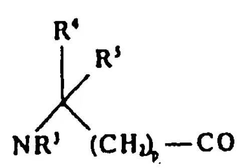


where p denotes the number 0 or 1, R^3 denotes hydrogen or methyl, R^4 and R^5 denotes cyclopentyl or straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by naphthyl or phenyl which in turn may be substituted by fluorine, chlorine or alkoxy with up to 4 carbon atoms, or substituted by imidazolyl, triazolyl, pyridyl or pyrazolyl, where the NH functions are possibly protected by methyl, benzyloxymethylene or t-butyloxycarbonyl (Boc), L and M are the same or different and stand for a direct bond or for a group of the formula

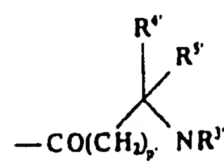


in which $R^{3'}$, $R^{4'}$ and $R^{5'}$ have the above reported meanings for R^3, R^4 and R^5 and are the same as or different from them, and R^9 is a straight-chained or branched alkyl with up to 4 carbon atoms, in there D or L form or as a D,L-isomer mixture, R^1 and R^2 are the same or different and stand for straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by cyclohexyl or phenyl, Y stands for hydrogen or for a group of the formula $-CO-R^{10}$ where R^{10} is a straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by pyridyl or phenyl, or alkoxy with up to 4 carbon atoms, for the radical R^{10} where R^{10} has the above-reported meaning, with the qualification that either

a) at least one of the amino acid radicals A, B, D or L or M stands for a group of the formula

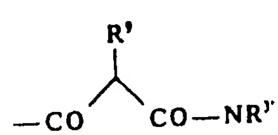


or



in which R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, p and p' have the above reported meaning and at least one of the substituents R^4, R^5, $R^{4'}$ or $R^{5'}$ stands for cyclopentyl or R^4 and R^5 or $R^{4'}$ and $R^{5'}$ in each case stand for methyl or

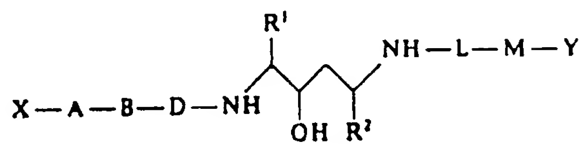
b) L or M must stand for the group of the formula



in which $R^{3'}$ and R^9 have the above reported meaning, and their physiologically unobjectionable salts.

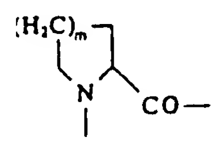
4. Compounds of general formula (I) as in claim 1 for use in controlling diseases.

5. Process for synthesizing compounds of general formula (I)

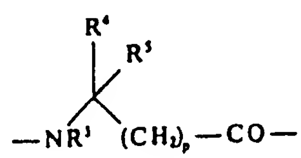


(I)

in which X stands for hydrogen or for alkoxy carbonyl or acyl in each case with up to 10 carbon atoms, A, B, and D are the same or different and in each case stand for a direct bond or for a radical of the formula

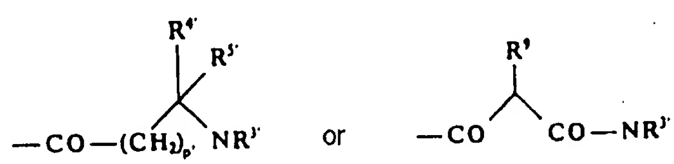


where m signifies the number 1 or 2 or stands for a group of the formula



where p denotes the numbers 0, 1 or 2, R^3 stands for hydrogen, a straight chained or branched alkyl with up to 8 carbon atoms or phenyl, R^4 and R^5 are the same or different and signify a 3 to 8 membered heterocycle with up to 4 hetero-atoms from the series of nitrogen, oxygen or sulfur, cycloalkyl with 3 to 8 carbon atoms, or in each case stand for hydrogen or straight-chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by

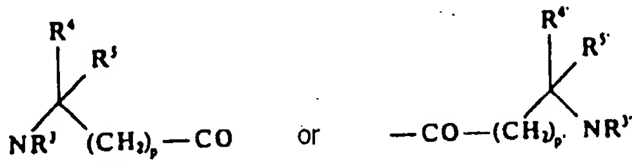
alkylthio with up to 6 carbon atoms, hydroxy, mercapto, guanidyl or by a group of the formula $-NR^6R^7$ or R^8-OC- where R^6 and R^7 are the same or different and denote hydrogen, straight chained or branched alkyl with up to 8 carbon atoms or phenyl, and R^8 denotes hydroxy, benzyloxy, alkoxy with up to 6 carbon atoms or the above-listed group $-NR^6R^7$, or alkyl which may possibly be substituted by aryl with 6 to 10 carbon atoms which in turn is substituted by hydroxy, halogen, nitro, alkoxy with up to 8 carbon atoms or by the group $-NR^6R^7$ in which R^6 and R^7 have the above-reported meaning or alkyl which is possibly substituted by a 5 or 6 membered nitrogen-containing heterocycle or indolyl where the corresponding -NH functions are possibly protected by alkyl with up to 6 carbon atoms or by an amino protective group, L and M are the same or different and stand for a direct bond or for a group of the formula



where p', $R^{3'}$, $R^{4'}$ and $R^{5'}$ have the above-reported meaning for p, R^3, R^4 and R^5 and may be the same as or different from them and R^9 is straight-chained or branched alkyl with up to 8 carbon atoms, in their D or L or as D,L isomer mixture, R^1 and R^2 are the same or different and stand for a straight chained or branched alkyl with up to 8 carbon atoms which is possibly substituted by cycloalkyl with 3 to 8 carbon atoms or aryl with 6 to 10 carbon atoms, Y stands for hydrogen or for a group of the formula $-CO-R^{10}$ where R^{10} is a straight chained or branched alkyl with up 8 carbon atoms which is possibly substituted by pyridyl or phenyl, or a straight chained or branched alkoxy

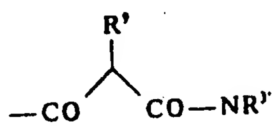
with up to 8 carbon atoms, or stands for the radical R^{10} where R^{10} has the above-reported meaning, with the qualification that either

a) at least one of the amino acid radicals A, B, D or L or M stands for a group of the formula

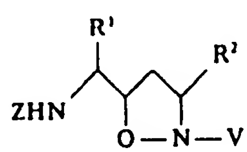


in which R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, p and p' have the above reported meaning and at least one of the substituents R^4, R^5, $R^{4'}$ or $R^{5'}$ stands for cyclopentyl or R^4 and R^5 or $R^{4'}$ and $R^{5'}$ in each case stand for methyl, or

b) L or M must stand for the group of the formula



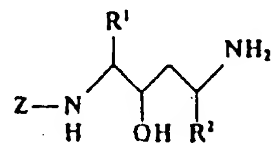
in which R^9 and $R^{3'}$ have the above reported meaning characterized by the fact that compounds of general formula (II)



(II)

in which R^1 and R^2 have the above reported meaning, Z has the above-reported meaning of X, but does not stand for hydrogen, or stands for one of the above-listed amino protective groups, and V stands for a radical capable of being split off hydrogeno-lytically such as benzyl, are reduced initially by

hydrogenolysis with opening of the isoxazolidine ring into the amino alcohols of general formula (III)



(III)

in which Z, R^1 and R^2 have the above-given meaning, if necessary subsequently condensed with compounds of general formula (IV) and (IVa)

HO-L'-M'-Y (IV)

HO-Y (IVa)

in which Y has the above-given meaning and the L' and M' have the above-reported meaning for L and M but do not stand simultaneously for a direct bond, if necessary in the presence of a water-removing accessory material and/or a base, and then, after the splitting off of the protective group Z, reacted by known methods with compounds of general formula (V)

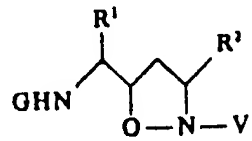
Z'-B'-D'-OH (V)

in which B' and D' have the above-reported meaning of B and D but do not stand simultaneously for a direct bond, Z' has the above-reported meaning of Z and is the same as or different from it, and in a last step after the splitting off of the protective group Z' are reacted with compounds of formula (VI)

X-A'-OH (VI)

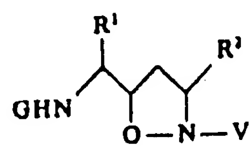
in which X has the above-reported meaning and A' the above-reported meaning of A but does not stand for a direct bond, if necessary in the presence of a base and inert organic solvents.

6. Compounds of general formula (II)

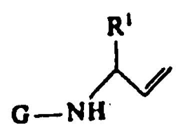
 (II)

in which R^1 and R^2 are the same or different and stand for a straight chained or branched alkyl with up to 8 carbon atoms which is possibly substituted by cycloalkyl with 3 to 8 carbon atoms or aryl with 6 to 10 carbon atoms, G stands for an amino protective group, and V stands for a radical that can be split off hydrogenolytically such as benzyl.

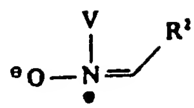
7. Process for the synthesis of compounds of general formula (II)

 (II)

in which R^1 and R^2 have the above reported meaning, G stands for the above mentioned amino protective group, and V stands for a radical that can be split off hydrogenolytically such as benzyl, characterized by the fact that compounds of general formula (VII)

 (VII)

in which G has the above reported meaning, are reacted in a cycloaddition reaction with compounds of general formula (VIII)



(VIII)

in which V and R^2 have the above reported meaning, if necessary in the presence of inert organic solvents.

8. Drugs containing at least one compound of general formula (I) as in claim 1.

9. Process for production of drugs characterized by the fact that at least one compound of general formula (I) as in claim 1 is brought into a form suitable for administration by using ordinary accessory materials and carriers.

10. Use of compounds of general formula (I) as in claim 1 in the production of drugs with a renin-inhibiting action.